REMARKS

Claims 24-36, and 38 are presently pending and under consideration in this application. Claims 39 and 40 are new. Support for new claims 39 and 40 can be found throughout the specification and specifically on page 4, lines 12-15. Claims 24, 28, 35 and 36 have been amended. Claim 37 formerly miss-numbered as a second claim 36 has been canceled. Support for the amendments to claims 24 and 35 can be found throughout the specification but in particular on page 4, lines 9-11. Support for the amendments to claim 36 can be found throughout the specification but in particular on page 1, lines 33-38 and on page 8, lines 29-33. No amendment should be construed as acquiescence in any ground of rejection.

35 USC § 102, Second Paragraph

Claims 28 and 29 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Examiner has asserted that Claim 28 drawn to a "knock out" is indefinite when it depends from claim 26 that is directed to a "vector." According to the Examiner, Claim 29 is included in this rejection because it depends from claim 28.

To clarify the invention, Applicant has amended claim 28 to depend from claim 24. Claim 29 continues to depend from claim 28. Applicant requests withdrawal of the rejection and reconsideration of the amended claims.

35 USC § 102, First Paragraph, Anticipation

Claims 24, 30, 31, 33 and 34 are rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of Chattopadhyay *et al.* (2000, Journal of Bacteriology, 182:6418-6423).

This rejection is respectfully traversed. The rejected claims are directed to methods of generating genetically modified yeast organisms for drug screening and include a step of introducing a heterologous gene encoding a protein or protein fragments. The cited reference is directed to yeast organisms where endogenous genes have been deleted. The homology of the genes involved to human genes does not matter, nor does the status of the genes as essential or nonessential. In view of the fact that claim 35 which is directed to a genetically modified yeast organism identified by the presence of a foreign gene and the reduction or elimination of compensating genes is regarded as being novel, it is not understandable, why claim 24 which is directed to a method for generating the new organism is not regarded as being novel. Therefore, this rejection should be withdrawn because the reference does not contain each and every element of the rejected claims.

Claims 24, 30-34, 38 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Hartman et al., 2001, Science, 291: 1001-1004 (Hartman).

Applicants respectfully request that this rejection should be withdrawn because the reference does not contain each and every element of the rejected claims. Hartman is not relevant for novelty of the present invention, as Hartman is a review article on the principles for buffering genetic variation. No specific organisms, genes, proteins or methods supporting the statements on the principles as outlined in Hartman are disclosed. The Examiner tries to find a basis for each of items a) to c) of claim 24 in Hartman and, however, fails, in doing so. In particular, with regard to claim 24, step a), the Examiner states that "*there is a need to study the relationship between a mutation and a gene that buffers the effect that the mutation has on the*

organism". However, this has nothing to do with the defined step a) of claim 24, which indicates that a foreign gene is introduced into the yeast organism. In Hartman only endogenous genes are addressed. The object of Hartman is to investigate the effect of the variation of one endogenous gene on other endogenous genes. However, in the present invention, a foreign gene encoding a protein which is of interest with respect to the finding of new active substances is introduced and the influence of this foreign gene on the yeast cell is investigated. Thus, the object of the present invention is directed to the generation of a drug screening system whereas Hartman investigates the principles of buffering of genetic variation. With regard to claim 24, step c), the Examiner recites the term "*it makes intuitive sense that if a process is weakened, then further inactivation of that process (or of a compensatory process) would bring its activity below some debilitating threshold*", which is also not in line with the present invention, as the reduction or elimination of compensating differentially regulated genes is applied only if these genes are up-regulated due to the introduction of the foreign gene. In view of the fact that claim 35 of the present invention is acknowledged as being novel over Chattopadhyay et al. due to the fact that the system only comprises the application of foreign genes/proteins, amended claim 24 should also be regarded as being novel in view of Hartman. As claims 25 to 38 are either dependent on claim 24 or refer thereto, also these claims should be regarded as being novel. Therefore, this rejection should be withdrawn because the reference does not contain each and every element of the rejected claims.

35 U.S.C. § 103(a), Obviousness

Claims 24-29, 32-36, 38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423 (Chattopadhyay) in view of Sauer, 1987, Molecular and Cellular Biology, 7: 2087-2096, (Sauer) previously cited, and Hartman et al., 2001, Science, 291: 1001-1004 (Hartman).

The Examiner newly rejects the claims as allegedly obvious in view of Chattopadhyay in view of Sauer and Hartman. The Examiner's reasoning seems to be the following: By combining Chattopadhyay disclosing the deletion of the btn1 gene and Sauer disclosing the cre-lox recombination system the Examiner concludes that deletion of the btn1 gene may be performed by introducing the cre-lox recombination system into yeast. Consequently, a foreign gene, namely the Cre gene, is introduced into a cell and upon disruption of btn1 gene via the cre-lox excision; the HSP30 and BTN2 genes are up-regulated. Hartman is apparently cited as providing motivation by teaching it "*would be desirable to study buffering relationships.*"

Applicants request that this rejection be withdrawn. As outlined above, a decisive difference between Chattopadhyay and the present invention is that in Chattopadhyay an endogenous gene, the btn1 gene, is actively disrupted, whereas it is a requirement of the present invention that a foreign gene is introduced into a yeast organism and the influence of the foreign gene on endogenous genes is investigated. The difference between the combination of Chattopadhyay and Sauer suggested by the Examiner when compared to the present invention is that the Cre gene does not directly induce modification of the expression of compensating differentially regulated genes. The cre-lox system acts only in combination with loxP sites which must, in addition to the Cre gene, be introduced into the yeast organism for the btn1 protein to be deleted. It is clear from the amended claims, if read in light of the specification, that the expression of the heterologous genes in the yeast directly results in the modification of the expression pattern of endogenous genes. In contrast to the scenario described by the Examiner it is not envisaged by the amended claims that additional systems are present which result in the deletion of endogenous genes which in turn modify the expression patterns of other endogenous genes. The system as proposed by the Examiner using Sauer requires the additional introduction of loxP sites allowing deletion of the sequence in between such loxP sites. Such a system is, however, not comprised by the present amended claim set which only requires the introduction of a foreign gene into a yeast organism. The scope of a claim should be interpreted in light of the specification. From the specification, it is unambiguously clear that introduction

of a foreign gene into an organism directly influences the expression pattern of endogenous genes without requiring that additional systems be interposed.

In order to clarify this difference in the claims Applicants have amended claim 24 with the phrase "*associated with*" within an additional wherein clause stating "*and wherein the heterologous expression is associated with the alteration of the expression pattern of endogenous genes*" as introduced into claim 24 (a). In the cited art, the expression of the foreign gene results in deletion of an endogenous gene, however, only with the aid of an additionally introduced deletion system. Only the variation of the expression pattern of this endogenous genes results in the variation of the expression pattern of other endogenous genes. Thus, the introduced foreign gene, namely the Cre gene, does not directly change the expression of endogenous genes. In view of the amendments and arguments presented here, Applicants request reconsideration of the amended claims and withdrawal of the rejection.

Claims 24-26 and 30-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi *et al.* (2000, FEBS Letters, 470:156-160) (Derisi), Gari *et al.*, (1997, Yeast 13:837-848)(Gari), and Wilson *et al.* (1999, PNAS, USA 96:12833-12838)(Wilson).

The Examiner has rejected the claims over DeRisi, Garí and Wilson where DeRisi allegedly discloses over expression of PDR1 and/or PDR3 in S. cerevisiae and identification of upregulated and down regulated genes. Moreover, the Examiner states that "*yeast of DeRisi meet the limitations of the claims with regard to proliferation.*" The Examiner further states that DeRisi's yeast "*would be readable on the claims because their phenotype of 'survaival' has not changed between growing yeast in normal media and drugged media.*" Gari allegedly teach "*tetracycline-regulatable promoter system, wherein tetracycline induces tetO-driven gene expression and induces expression of a gene of interest.*" Wilson, allegedly teaches "*changes in gene expression following treatment with a drug.*"

This rejection is respectfully traversed. DeRisi teaches yeast strains which show a detectable phenotype which clearly constitutes a difference compared to the present invention. Applicants reiterate that the present invention is directed to situations where expression of a foreign heterologous protein does not produce any detectable change of any phenotype that is perceptible. Applicants also point out that DeRisi does not involve introducing foreign genes but instead deletes the endogenous Pdr genes and subsequently reintroduces mutated forms of the endogenous genes. Applicants have amended claim 24 to further clarify and describe the invention by indicating that the expression of the foreign gene does not produce any detectable change of any phenotype perceptible from the outside. This amendment indicates that not only a specific phenotype, such as over-proliferation or survival, is addressed and investigated, but that the sum of all phenotypes as they are perceptible is addressed. Claim 24 now states "[a] *method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: (a) causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a foreign gene into the yeast organism having a phenotype, wherein the expression of the at least one protein or protein fragment does not produce any detectable change of any phenotype perceptible from outside of the yeast organism, wherein a detectable change of the phenotype that is perceptible from outside of the yeast organism comprises the behavior of the yeast organism, the morphology of the yeast organism, or a combination thereof, and wherein the heterologous expression is associated with the alteration of the expression pattern of endogenous genes; (b) analyzing the modified gene expression pattern and identifying compensating differentially regulated genes; and (c) phenotyping the*

yeast organism wherein phenotyping is carried out following the reduction or elimination of compensating differential expression perceptible from the outside of the yeast organism.

Applicants have also amended claims 35 and 36 to more clearly describe the invention. Amended claim 35 is directed to "*a genetically modified yeast organism, comprising: (a) a genetically modified expression of at least one foreign gene, which is associated with results in compensating differential expression of at least one gene endogenous to the modified yeast organism; and (b) a phenotype caused by the reduction or elimination of the compensating differential expression of the gene, wherein the phenotype is perceptible from outside of the modified yeast organism and comprises behavior of the yeast organism, the morphology of the yeast organism, or a combination thereof.*" Amended claim 36 is directed to a "*method for identifying a substance having an effect on the function of a heterologously expressed protein or protein fragment, which method comprises the steps of: (a) contacting the substance with the genetically modified yeast organism of Claim 34 or Claim 35; and (b) measuring the change in the modified yeast organism as compared to a genetically unmodified yeast organism; wherein change is the change of behavior of the modified yeast organism, the morphology of the yeast organism, or a combination thereof.*"

In conclusion, Applicants contend the present invention cannot be compared successfully to DeRisi. As described in the amended claims, the present invention is directed to methods for generating modified yeast organisms and modified yeast organisms where a foreign gene is introduced into the yeast organism and is expressed or overexpressed, however, in DeRisi *et al.*, an endogenous gene is mutated. Thus, the two systems are totally different: in the system of the present invention, the effect of a foreign

gene on a cell is the subject, whereas in the system of DeRisi *et al.* the effect of a mutated endogenous gene on the cell is the subject. In view of this fundamental difference, the claims as presently amended are unobvious and are patentable over DeRisi, Garí and Wilson and applicants request reconsideration and withdrawal of the rejection.

Fees

No additional fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant application. The claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 908-231-2597.

Respectfully submitted,

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